REMARKS

Applicants have carefully studied the Office Action mailed on June 3, 2003, which issued in connection with the above-identified application. The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Pending Claims

Claims 1-22 are pending and at issue in the application. Claims 20-22 have been withdrawn from consideration as drawn to a non-elected invention. Claims 1-3 and 5 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and under 35 U.S.C. § 102(b) as being anticipated by Lohmann *et al.* (Science, 1999, 285:110-113) and PCT Publication No. WO 98/39031.

Claim 1 has been canceled without prejudice or disclaimer. Claim 2 has been re-written in independent format, and is of the same scope as claim 2 as filed. Newly introduced recitation "wherein said nucleic acid contains at least one mutation in the HCV sequence" finds support, for example, at page 13, lines 11-24, page 17, line 22 - page 18, line 11, page 26, lines 9-17, page 29, line 28 - page 30, line 9, Example 1 (especially page 40, lines 9-18 and Table I at pages 40-41), and the original claims 6-11. Claim 6 has been re-written in dependent format (as dependent from claim 2). Claims 3, 5 and 12 have been amended to correct dependency from canceled claim 1. Claim 4 has been amended to correct formal defects. No new subject matter has been added as a result of these amendments, no new search is required, and no new issues are raised.

Restriction Requirement

In the Office Action, despite the applicants' arguments presented in the Response to the Restriction Requirement of January 28, 2003, the Examiner maintained the Requirement for Restriction and refused to rejoin the claims of the provisionally elected Group I (claims 1-3 and 5) with the claims of Group II (claims 6-11) and Group III (claims 4 and 12-19).

Applicants respectfully note that, in the Restriction Requirement of January 28, 2003 (paper 10), the Examiner incorrectly recites that Group III drawn to cell lines transfected with nucleic acid molecules includes only claims 4 and 12-13. Dependent claims 14-19 directed to cell lines are completely missing from the Restriction Requirement. Applicants also note that, due to an inadvertent drafting error, claim 4 as currently pending is directed to a cell line. This lead to it being grouped with the claims of Group III. As amended above, claim 4 is now dependent on claim 2 and is directed to a nucleic acid. Claim 4 as amended should be therefore placed in Group I.

With respect to maintaining the Restriction Requirement between claims of Groups I-III (claims 2-19 as amended), applicants respectfully disagree with the Examiner and note that, in the Restriction Requirement, the Examiner does not explain why the nucleic acids recited in claims 6-11 (Group II) are different from the nucleic acids recited in claims 2-5 (Group I). The Examiner merely states in the description of the groups on page 2 of the Restriction Requirement that the claims of Group II are directed to nucleic acid molecules encoding a fragment of HCV. Applicants respectfully note that the claims of Group I encompass such fragments. In particular, claim 2[1] recites nucleic acid molecules having the same general elements as the nucleic acid

[1] In the amendment provided above, claim 1 has been canceled and claim 2 remained the only independent claim directed to nucleic acids.

molecules recited in claims 6-11 (*i.e.*, 5' HCV non-translated region (NTR), a heterologous gene, at least a portion of HCV polyprotein coding sequence, and 3' HCV NTR.). To clarify this, claim 6 has been amended to depend from claim 2.

With respect to claims 12-19 directed to cell lines, applicants respectfully submit that the cell lines recited in these claims are transfected with the isolated nucleic acids recited in the claims of Group I. Indeed, these claims as amended depend from claim 2. Applicants further note that it is a standard practice in Group 1600 to examine cells comprising a recombinant nucleic acid together with said nucleic acid. For example, U.S. Patents No. 6,392,028 and 6,127,116 submitted herein as part of the Supplemental IDS (examined by Examiners Caputa, Elliott and Larson, all of Group 1600) contain claims directed to both HCV-derived nucleic acids and cells comprising such nucleic acids. *See* also 35 U.S.C. § 103(b).

In the applicants' response to the requirement for sequence election in the Restriction Requirement of January 28, 2003, SEQ ID NO: 4 was elected with traverse. Applicants respectfully request that the requirement for sequence election be withdrawn. In contrast to the Examiner's statement at page 2 of the Restriction Requirement, the requirement for sequence election is believed to be a species election. Claims 6-11 as amended depend from claim 2 (which due to cancellation of claim 1 is the only independent claim directed to nucleic acids). As noted above, claims 6-11 recite nucleic acid molecules having the same general elements as the nucleic acid molecule recited in claim 2. Accordingly, the nucleic acid sequences recited in claims 6-11 are species of the genus nucleic acid recited in claim 2. The fact that these nucleic acid species are distinguishable from each other in their sequence and the growth rate of host cells transfected with them is a necessary feature of being a species of a genus.

In the applicants' response to the requirement for cell line election in the Restriction Requirement of January 28, 2003, Huh-7 cell line was elected with traverse. Applicants respectfully request that the requirement for cell line election be withdrawn. In contrast to the Examiner's statement at page 2 of the Restriction Requirement, the requirement for cell line election is believed to be a species election. Applicants respectfully note that all cell lines recited in claims 13-19 are species of the genus recited in claim 12, which are all transfected with the nucleic acid of claim 2. Furthermore, HCRV 2, HCVR 8, HCVR 9, HCVR 22, and HCVR 24 are all species of Huh-7 cells transfected with the nucleic acid of claim 2. The genus host cell recited in claim 12 embraces all of these species, and the Examiner does not provide any evidence or reason to dispute this.

In light of the foregoing arguments, applicants respectfully request that the Requirement for Restriction between claims 2-19 as amended be withdrawn and the claims examined for all sequences and cell lines they encompass.

35 U.S.C. § 112, First Paragraph Rejections

In the Action, claims 1-3 and 5 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner contends that the present specification, while being enabling for an isolated nucleic acid molecule encoding HCV genome I377/NS3-3'UTR and having, as a result of a long-term propagation in culture, some particular mutations that enable it to replicate efficiently without reducing the host cell growth rate by more than 10-fold, does not provide enablement for a genus of nucleic acid molecules encoding any full or partial HCV genome that is able to replicate efficiently when transfected into a susceptible cell line without reducing the growth rate of such cell line by more than 10-fold.

As claim 1 has been canceled, the rejection of this claim is rendered moot. With respect to claims 2-3 and 5, the rejection is respectfully traversed. In contrast to the Examiner's assertion, applicants respectfully note that claims 2-3 and 5 as amended encompass not the full universe of heterogeneous HCV-derived nucleic acids, but only those HCV-derived nucleic acids which

(i) encode a replication competent recombinant HCV genome,

(ii) comprise from 5' to 3' on the positive-sense nucleic acid a) a functional 5' HCV NTR comprising an extreme 5'-terminal conserved sequence, b) at least one open reading frame (ORF) encoding a heterologous gene operatively associated with an expression control sequence, wherein the heterologous gene and expression control sequence are oriented on the positive-strand nucleic acid molecule, c) an ORF encoding at least a portion of an HCV polyprotein whose cleavage products form functional components of HCV virus particles and RNA replication machinery, and d) an HCV 3' NTR comprising an extreme 3'-terminal conserved sequence, and

(iii) are able to replicate efficiently when transfected into a susceptible cell line without reducing the growth rate of said cell line by more than 10-fold.

As acknowledged by the Examiner at page 2 of the Office Action, the present application provides a detailed disclosure of various replication competent nucleic acid molecules derived from HCV I377/NS3-3'UTR and having mutations that lead to their efficient replication in host cells without reducing the host cell growth rate by more than 10-fold. All of these molecules comprise the above-identified structural and functional elements encompassed by the present claims. Applicants respectfully submit that, in light of the current law and patent practice, the disclosure of such specific nucleic acid molecules derived from HCV I377/NS3-3'UTR provides a sufficient number of examples of the nucleic acid molecules encompassed by claims 2-3 and 5.

It is believed that the Examiner imposes an overly high and burdensome duty on applicants, one not required by Section 112 or by the case law[2]. Thus, according to the current law and patent practice, the specification can permit some inferences to be drawn by those skilled in the art, and still comply with the enablement and written description requirement. In other words, there is no requirement that the claims be restricted to the working examples. Section 2164.03 of MPEP recites:

> the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required (*In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir., 1991); *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971))

As further stated in section 2164.08 of MPEP:

> claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for non-inclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious (*In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970))... When analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification.

See also *Application of Angstadt* (537 F.2d 498, 502-503, 190 USPQ 214, 218 [Cust. & Pat.App., 1976]) stating that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art." Similarly, in *In re Rasmussen*, court stated that "a claim may be broader than the specific embodiment disclosed in a specification" (650 F.2d 1212,

[2] *See*, in particular, *In re Wands*, 858 F.2d 731-40, 8 USPQ2d at 1400-07 (Fed. Cir. 1988).

1215, 211 USPQ 323, 326 [Cust. & Pat.App., 1981]). Finally, in *In re Goffe* (542 F.2d 564, 567, 191 USPQ 429, 431 [CCPA 1976]), the court stated:

> To provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Applicants further note that, as follows from the Office Action, the Examiner has misunderstood the concept of selection which is central to understanding and evaluating the present invention. Thus, the Examiner states at page 3 of the Office Action that it is very unpredictable that every construct encompassed by the present claims will be able to replicate efficiently without reducing the host cell growth rate by more than 10-fold, because the HCV genome has high level of heterogeneity, with some genomes being more toxic to the host cells than others or replicating less efficiently than others. In response. applicants respectfully submit that one of the novel aspects of the present invention is a selection method which allows to overcome the unpredictability of the replication efficiency and toxicity of the HCV-derived nucleic acids to their host cells. As specified, *e.g.*, at page 29, line 28 - page 30, line 5, page 35, lines 11-30 and page 38, lines 19-22, the present application discloses a culturing and selection methodology involving prolonged propagation under stringent selection conditions resulting in generation of "adapted" HCV-derived nucleic acids harboring mutations, which allow their efficient replication in a particular host cell (which might have also acquired some "adaptive" characteristics as compared to a non-transfected cell), without reducing the growth rate of the host cell by more than 10-fold.

In contrast to the Examiner's assertion at page 5 of the Office Action that the disclosed

culturing and selection methodology requires undue experimentation because it is unpredictable, applicants respectfully note that the selection methodology of the invention is fully described and enabled by the present specification. As disclosed, *e.g.*, in Example 1 (*see*, in particular page 35, lines 11-30), this selection methodology involves the use of (i) specific selective conditions (*e.g.*, specific concentration of selective drug) and (ii) specific length of imposing such conditions. This general methodology is the same irrespective of a particular HCV-derived nucleic acid or a cell line used and works by selecting only those combinations of nucleic acids and host cells that allow efficient nucleic acid replication and host cell growth. The nature of every selection methodology is precisely that one does not need to know specific properties of a given input nucleic acid or a host cell. The selection works by eliminating all nucleic acids and host cells that do not possess the desired properties.

Applicants respectfully submit that the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). *See*, also, *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The selection methodology disclosed in the present application is novel. However, applying it to obtain additional HCV-derived nucleic acids encompassed by the present claims would not require more than routine cell culture and virology techniques.

In the Action, the Examiner further states that the present application does not provide sufficient amount of guidance to teach any isolated nucleic acid molecule encoding a full-length HCV genome or other partial HCV genome other than a nucleic acid molecule encoding from

NS2 to the 3' end. The Examiner also states that the present application does not teach any cell line susceptible for the HCV-derived nucleic acid transfection and replication other than Huh-7. In response, applicants respectfully submit that, in light of the present disclosure of the HCV genome structure (provided, *e.g.*, at pages 2-4 and Figure 1 of the specification) and methods for construction of recombinant HCV replicons (provided, *e.g.*, at pages 25-28 of the specification) as well as various cell lines susceptible to HCV propagation (provided, *e.g.*, at pages 9-11 an page 28, lines 15-21 of the specification), one skilled in the art would readily be able to identify and design all HCV-derived sequences and cell lines encompassed by the present claims, *i.e.*, this is within the knowledge of those skilled in the art and need not be described in greater detail.

In light of the above-presented standards and arguments, it is believed that the present application provides an adequate enablement for the full range of nucleic acids encompassed by claims 2-3 and 5. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, is believed to be overcome and withdrawal of such is kindly requested.

35 U.S.C. § 102(b) Rejections

In the Office Action, the Examiner has rejected claims 1-3 and 5 under 35 U.S.C. § 102(b) as being anticipated by Lohmann *et al.* (Science, 1999, 285:110-113) and PCT Publication No. WO 98/39031 (Rice *et al.*).

As claim 1 has been canceled, the rejection of this claim is rendered moot. Claims 3 and 5 have been amended to depend from claim 2. Although, at page 5 of the Office Action, only claims 1, 3 and 5 are stated to be rejected over Lohmann *et al.*, the present response also addresses the rejection of claim 2.

In the Action, the Examiner contends that Lohmann *et al.* use the same starting HCV-derived construct and Huh-7 cell line as encompassed by the present claims. The Examiner further states that, while Lohmann *et al.* teach that the replication of the HCV-derived construct in Huh-7 cells reduces their doubling time at 3-5 weeks post-transfection, they do not particularly teach that the reduction is so significant that it is more than 10-fold lower than the growth rate of parental non-transfected cell line. The Examiner continues with the argument that the increased growth rate of the selected clones of the present invention is simply the result of the increase in cell density and that, if Lohmann *et al.* kept their culture growing long enough, sooner or later they would have observed the same phenomena.

The rejection is respectfully traversed. Applicants respectfully submit that Lohmann *et al.* do not anticipate the present invention, because, in contrast to the Examiner's assertion, they do not disclose or suggest to incubate their clones longer under specific selection conditions to achieve the selection of "adapted" HCV clones encompassed by the present claims. On the contrary, they teach away from the present invention by stating in the last column of the article (page 112) that the formation of "adapted" replicons and cell clones under conditions of their experiments is highly unlikely, because (i) the sequence analysis of several replicons recloned from two different cell clones did not reveal consistent mutations and (ii) upon serial passage of the replicons in naïve Huh-7 cells, no significant increase of the number of colonies was observed. The Examiner's attention is also directed to page 39, line 31 - page 40, line 8 of the present application, where the differences between Lohmann *et al.* and the present invention are discussed in great detail.

Applicants respectfully note that the subsequent articles published by Lohmann *et al.* and their co-workers (group of Ralf Bartenschlager at the Institute for Virology at Johanes-Gutenberg University in Mainz, Germany) provide a further proof that, at the time the cited Lohmann *et al.*

reference was published, its authors did not possess or even suspect the existence of "adapted" replicons. It was only after the filing date of the present priority application, when the authors of Lohmann *et al.* and their colleagues obtained several "adapted" replicons having similar characteristics to the replicons disclosed in the present application. The fact that it took them almost two years to identify such "adapted" replicons clearly indicates that, in contrast to the Examiner's assertion, the proper selection process was not established at the time of Lohmann *et al.* reference and the "adapted" replicons did not simply emerge by keeping the culture growing long enough. Indeed, as stated in Lohmann *et al.* article published in 2001 (J. Virol., 75: 1437-1449, 2001, page 1445, left col., ¶ 2 and page 1438, left col., ¶ 2, attached as Tab 3) in reference to their earlier and present work (emphasis added):

> The recent development of selectable subgenomic HCV replicons has opened new avenues to the study of HCV replication, persistence, and pathogenesis in cultured cells. However, owing to the small number of HCV RNA-containing cell colonies routinely obtained, the system was of limited use for studies using reverse genetics methodologies. In a search for the reasons for this low efficiency, we found that HCV RNAs must first acquire adaptive mutations that, as shown by the highly adaptive mutation within NS5B, can increase the ECF by up to 3 orders of magnitude.
>
> In this study, we analyzed the replicating HCV RNA species in selected cells and provide direct experimental proof that these RNAs carry adaptive mutations.

With respect to the rejection over WO 98/39031 (Rice *et al.*), the Examiner states that WO 98/39031 discloses a genetically engineered replication-component HCV nucleic acid clone, which comprises from 5' to 3' a functional 5' NTR with extreme 5'-terminal conserved sequence, an ORF encoding at least a portion of an HCV polyprotein, 3' NTR comprising an extreme 3'-terminal conserved sequence, and a heterologous gene operably associated with an expression control sequence. The Examiner contends that WO 98/39031 also teaches (i) a

method of producing HCV virus particles comprising transfection of a human hepatocyte cell line with HCV DNA or its transcript and that (ii) right after transfection, most cells died, but a G418 (inserted drug resistant gene) population grew up over the course of a few months with HCV RNA still present in these cells. The Examiner concludes that the characteristic of reducing the cell growth if exist in the disclosure of WO 98/39031, is only a temporary phenomena.

Applicants respectfully traverse the rejection and note that WO 98/39031 does not anticipate the present invention, because it does not disclose or suggest to incubate the HCV clones longer under specific selection conditions to achieve the selection of "adapted" HCV clones encompassed by the present claims.

The subsequent articles published by the inventors of WO 98/39031 and their co-workers provide a clear proof that, at the time WO 98/39031 was filed (February 26, 1998), they did not possess or even suspect the existence of "adapted" replicons. It was only more than two years later (*i.e.*, after the filing date of the present priority application), when the inventors of WO 98/39031 and their colleagues obtained several "adapted" replicons having similar characteristics to the replicons disclosed in the present application (*see* Blight *et al.*, Science, 290: 1972-1974, December 2000, attached as Tab 4). The fact that it took them so long to identify such "adapted" replicons clearly indicates that, in contrast to the Examiner's assertion, the proper selection process was not established at the time of filing of WO 98/39031 and the "adapted" replicons did not simply emerge by keeping the culture growing long enough. In fact, as follows from the published interview of Rice, one of the inventors of WO 98/39031, it was not until the development of the HCV constructs disclosed in the cited 1999 Lohmann *et al.* reference (published after the filing date of WO 98/39031) that he and his co-workers were able to obtain

their "adapted" replicons. Specifically, as stated in the review by Marshall accompanying Blight *et al.* article (Science, 290: 1870-1871, December 2000, attached as Tab 5):

> Rice, now at Rockefeller University in New York City, says his replicon builds on earlier work by Ralf Bartenschlager and colleagues at the Institute for Virology at Johanes-Gutenberg University in Mainz, Germany. In work reported last year (Science, 2 July 1999, p. 110), Bartenschlager's team took the HCV genome apart and reassembled it into a replicon, editing out parts and adding new pieces, including an antibiotic resistance gene that can be used to select the cell clones that produce the viral proteins.
> ... [A]ccording to Rice, Bartenschlager's initial system is inefficient, producing HCV proteins in only about one in a million host cells.
> To improve the efficiency, Rice and Blight rebuilt the system using Bartenschlager's data from GenBank, looking for genetic mutations that might enable the replicon to be more productive...

It follows, that the mutant HCV replicons adapted to grow in culture with high efficiency disclosed in the present application cannot be anticipated by WO 98/39031.

Applicants further note that, when interpreting Lohmann *et al.* reference and WO 98/39031, the Examiner cannot rely on the concept of inherency. As stated in MPEP 2112, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ 2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

The analysis of the case law on the subject of inherency demonstrates that the Examiner has not established a prima facie case of anticipation. Thus, that the prior art product may

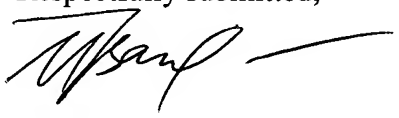
possibly have the same features as the claimed invention will not substantiate a finding of inherency. Rather, inherency must flow as a necessary conclusion from the prior art, not simply a possible one. *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however may not be established by probabilities or possibilities. *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950-51 (Fed. Cir. 1999).

In summary, none of the references cited by the Examiner anticipate the present invention. Reconsideration and withdrawal of the anticipation rejection is believed to be in order.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 2-19 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,



Dated: November 20, 2003

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